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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/643,755	08/23/2000	Gijs van Rooijen	9369-153/MG	1008

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EXAMINER	
HELMER, GEORGIA L	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/643,755	VAN ROOIJEN ET AL.	
	Examiner	Art Unit	
	Georgia L. Helmer	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-17 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-17 and 21-23* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 May 2004 has been entered.

2. Claims 1,3, 5-17 and 21-23 are pending, and are examined in this Office Action.

3. The 37 CFR §1.132 Declaration of David Dennis, dated 26 May 2004, is acknowledged.

4. All rejections not addressed below have been withdrawn.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

6. Claims 2-4, 8, 11, 17-22 and 24-28 are objected to because the status identifier of the claims is improper according to 37 CFR 1.121. "Deleted" is not a permissible status identifier; "Canceled" is a proper status identifier. Claims 8, 11, 17, 21 and 22 are

objected to as having improper status identifiers; "previously amended" is improper, "previously presented" is proper. See the attached Interview Summary.

Correction is required.

Claim Rejections - 35 USC § 112-second

7. Claims 14-16 are rejected under 35 U.S.C. 112, because in claims 14-16, "said total seed protein" lacks antecedent basis.

Correction or clarification is required.

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-12, 14-17 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method using Brassica napus cells does not reasonably provide enablement for any plant cell.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Applicant's invention involves a method for the production of chymosin involving recombinant expression of chymosin in plant seeds, and a method for the isolation of chymosin from the seeds.

The enablement issue is *any seed of any plant.*

Applicant's claims are broadly drawn to all plants including taxonomically divergent plants including Angiosperm (flowering plants) woody trees including fruit trees, as well as Gymnosperm (non-flowering plants) woody trees including pine and blue spruce, ferns as well as Eucalyptus species, or unspecified plants, including taxonomically divergent plants including Angiosperms (flowering plants) including corn, rice, sunflower, fruit trees, as well as to Gymnosperms (non-flowering plants) including pine and blue spruce, as well as ferns.

Re *any seed of any plant:* Applicant claims method of isolated chymosin from seed of any transgenic plant (produced by claim 1). Applicant teaches a method of

isolation from Brassica napus seed. Protein isolation and purification take into account two kinds of factors: (i) separation of the protein of interest from a particular biological source, and (ii) the biochemical properties of the particular protein. It is well known in the art that plant seed development and the location and composition of the various stored components vary among seeds of different species. (Buchanan, et al. Biochemistry & Molecular Biology of Plants (2000) American Society of Plant Physiologists, Rockville Mad 20855, pages 1024-1028, and Table 19.2). It is unpredictable that a method of enzyme purification developed for Brassica napus seed, composed of 48% oil, 19% carbohydrate, and 21% protein, with the major storage organ being the cotyledons, would function as desired for maize seed, with 5% oil, 80% carbohydrates, and 10% protein, with the major storage organ being the endosperm, or for any other plant, with reasonable expectation of success. Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

In view of the breadth of the claims (any plant, any plant seed, any seed-specific promoter, any chymosin-encoding sequence), the lack of guidance in the specification, undue trial and error experimentations would be required to enable the invention as commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

9. Claims 1, 3, 5-17 and 21-23 are rejected under 35 U.S.C. 103 as being unpatentable by Willmitzer et al (WO 92/01042) in view of applicant's admitted prior art.

Willmitzer teaches a method for the production of chymosin in a plant seed comprising introducing into tobacco and potato plant cells a chimeric nucleic acid sequence comprising a seed-specific phaseolin promoter, a nucleic acid sequence encoding pro-peptide chymosin, and a terminator, then growing the plant until it sets seeds and obtaining chymosin-containing seeds (Abstract, p 4, 5, 10 and 13). Seeds obtained from the transgenic plants are tested to assure that the gene of interest is present. The expressed enzyme can be isolated from the seed (p 3). Willmitzer further teaches including a plant signal sequence (p 5). The pro-chymosin of Willmitzer appears to a mammalian chymosin obtainable from a bovine, sheep, or goat source (p.13), since these are the only know nature sources of chymosin (specification, p.1). Willmitzer teaches the production of 0.1% - 0.5% chymosin of the total soluble protein (p. 14, lines 30-32). Since the method of Willmitzer is the same as Applicant's method, and teach the same promoter as preferred by Applicant, the percentage yields would have been an inherent property of the DNA construct used. If Applicant's percentage yields are different from that of Willmitzer, it is suggested that Applicant amend the claims and include specific structures such which would account for this difference.

Willmitzer further teaches a method of isolating chymosin by crushing (p 12, line 10) plant tissue, fractionating the resulting product (p 12, lines 9-15), contacting this product with a protein binding resin (p 12, lines 20-25).

While Willmitzer teaches the inclusion of a plant signal sequence and terminator in a chimeric construct, Willmitzer does not specifically teach a tobacco PR-S signal sequence and phaseolin terminator. However, the inclusion of a heterologous signal

sequence and terminator in a chimeric construct was notoriously well know in the art, as evidenced by the numerous examples set for by Willmitzer (p. 5) as well as by Applicant (p. 9 and 12). Applicant's admitted prior art indicates that a tobacco PR-S signal sequence and phaseolin terminator, as well as their biological properties, were also known at the time the invention was made (p. 9 and 12). Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize any of the known plant signal sequences and terminators of the prior art, including the claimed tobacco PR-S signal sequence and phaseolin terminator, for their know biological properties, in the chimeric construct for expressing the chymosin of Willmitzer without any surprising or unexpected results. One skilled in the art would have been motivated to generate the claimed invention with a reasonable expectation of success.

Methods of protein purification of recombinant plant proteins were well known in the art : See Cramer et. al. (p. 95-118, especially p. 162, 1st ¶, in Plant Biotechnology: New products and applications, 1999, ed. Hammond et. al., Springer, New York).

Applicant traverses (Response 27 May 2005, p. 8-9) saying primarily that the Cramer et. al. reference, p. 107, states that "methods of efficiently recovering proteins from the apoplastic fluid have yet to be developed". Applicant's traversal is unpersuasive. None of the claims are drawn to protein recovery from apoplastic fluid.

While it is known that seeds can be fractionated into three fractions (oil, aqueous, and insoluble) based on water solubility, Willmitzer does not teach contacting the aqueous fraction with the protein binding resin. However it is well known that proteins

are polyelectrolytes, having multiple positive and negative-charged ionic groups. And that given the phases of oil, water and insoluble, proteins would be found in the aqueous phase. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to take the aqueous phase, for its known biochemical properties, and contact it with the protein binding resin of Willmitzer, to generate the claimed invention, without any surprising or unexpected results.

While Willmitzer teaches methods of protein isolation using a protein binding resin, he does not specifically teach hydrophobic interaction resins. However, it is well known that proteins are amphipathic molecules, having both strongly polar and strongly nonpolar groups. Applicant's admitted prior art indicates that hydrophobic interaction resins and ion-exchange resins were known at the time the invention was made (p. 23, 24, specification). Accordingly it would have been prima facie obvious to one of ordinary skill in the art of the time the invention was made to contact the aqueous fraction, with a hydrophobic interaction resin, for its know biochemical and physical properties, to generate the claimed invention, without any surprising or unexpected results.

While Willmitzer teaches methods of protein isolation using a protein binding resin, he does not specifically teach ion-exchange resins. However it is well known that proteins are polyelectrolytes, having multiple positive and negative-charged ionic groups. Accordingly it would have been prima facie obvious to one of ordinary skill in the art of the time the invention was made to contact the aqueous fraction, with an ion-

exchange resin, for its know biochemical and physical properties, to generate the claimed invention, without any surprising or unexpected results.

10. The Declaration of David Dennis has been thoroughly considered and is found unpersuasive. The Declaration of Dennis, dated 26 May 2004, states (p. 2) his opinion that the expression of chymosin in seed at a level in excess of 0.5% is a significant advance over Willmitzer even without further limitation of the purification method. Dennis (item 9, p. 2) states that Willmitzer teaches chymosin produced in tobacco leaves and in potato tubers, however "no evidence is presented that shows the integrity of the chymosin protein and no attempt is made to purify the protein to homogeneity". Dennis further states (p. 3 –item 11) that "the purification of a protein from plant tissue to homogeneity is not a simple or routine task. It is something that has to be developed for each protein that is isolated".

The Declaration of Dennis is unpersuasive. None of the claims is drawn to purification of chymosin to homogeneity, nor are the claims drawn to chymosin with any particular biological activity or structure. The claims are not drawn to protein quantities greater than 0.5%. And 0.5% is taught by the prior art.

Remarks

11. No claims are allowed

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 571-272-0796. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

P Phuong Bui 6/15/05

Georgia Helmer PhD
Patent Examiner
Transgenic plants – Art Unit 1638
5 June 2005

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PRIMARY EXAMINER